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Therapeutic strategies against epilepsy in Mediterranean countries: a report from an international collaborative survey

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A collaborative survey was performed to compare prescribing strategies for the treatment of epilepsy in Mediterranean countries, based on analysis of 500 questionnaires compiled by physicians in 14 different countries. For partial seizures, carbamazepine was the drug of choice in most countries, whereas the second choice of drug differed widely. For primarily generalized tonic–clonic seizures, valproic acid was usually preferred, but other drugs used widely in some countries included phenobarbital, phenytoin and carbamazepine. Lamotrigine was the most popular second-line drug for primarily generalized tonic–clonic seizures in the European countries. In patients where the initial drug failed, switching to an alternative monotherapy was usually the preferred strategy, but advocates of early use of combination therapy exceeded 30% in the respondents of seven countries. Most respondents, in all countries except Turkey, did not prescribe drugs to prevent recurrence of febrile seizures; however, intermittent prophylaxis with a benzodiazepine was advocated by a considerable number of physicians, and continuous prophylaxis was prescribed by a significant minority of respondents in France, Syria and Tunisia. New drugs were rarely used as first-line treatment due to high cost and inadequate experience. Overall, this survey indicates that there is a wide variability in therapeutic practices between and within countries. This information may be useful for the implementation of national educational activities and for the design of pragmatic trials aimed at comparing different therapeutic strategies.

Key words: antiepileptic drugs; epilepsy; pharmacoepidemiology; drug utilization.

INTRODUCTION

Choice of treatment of epilepsy is influenced by many factors. These include efficacy of the various drugs in different seizure types and syndromic forms, their comparative tolerability profile, interactive potential and ease of use, factors related to the characteristics of the patient, and cost and reimbursability considerations[1–4]. However, cost-benefit ratios of different treatments are difficult to quantify objectively[5], and individual perceptions about the comparative value of the various drugs differ considerably. Therapeutic strategies may vary widely from one country to another[6–9] depending on the structure of the national health system, sociocultural background, drug availability and, not least, commercial pressure. Because of its extreme diversity in social, cultural and medical background, the Mediterranean region offers a unique opportunity to study national differences in therapeutic practices and their relation to local factors. Since 1990, physicians from this region with a special interest in epilepsy have held regular meetings aimed at comparing their experiences and building a collaborative network to improve the care of people with epilepsy. Within the framework

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of these activities, it was considered of interest to compare therapeutic practices in this area. The survey saw participation from almost 500 physicians from over 10 countries, and its results are summarized in this report.

MATERIALS AND METHODS

The survey was conducted between January and November 1997 and involved distribution of a questionnaire designed to evaluate the pattern of prescription of antiepileptic drugs by individual doctors in different situations. Prior to distribution, the questionnaire was translated into the local language and mailed by a national coordinator to all physicians known to have an active interest in the management of epilepsy. In some countries with an established chapter of the International League against Epilepsy (Algeria, France, Greece, Israel, Italy, Spain, Tunisia and Turkey), mailing was extended to all members of the chapter. Although these could include personnel not directly involved in clinical management, return of questionnaires was solicited only from physicians active in the day-to-day treatment of patients with epilepsy.

Specific issues addressed in the questionnaire included: (i) first-line and second-line drugs prescribed by the respondent for patients with partial seizures and primarily generalized tonic–clonic seizures; (ii) therapeutic strategy in patients refractory to initial treatment; (iii) management policy in children with uncomplicated febrile convulsions; (iv) first-line and second-line utilization of new drugs, and attitude towards the use of new antiepileptic drugs in general. In addition, information was collected about the qualification, professional experience and working practice of each respondent.

All questionnaires were forwarded to the central coordinators (EE and EP) for data processing and analysis. All results are reported descriptively.

RESULTS

Source of returned questionnaires

A total of 500 questionnaires from 14 different countries were returned (Table 1). The largest number of returns in absolute terms, with over 80 respondents, were from Italy, France and Tunisia. Responder rates as a percentage of distributed questionnaires was rather variable and ranged from 6% in Spain to 85% in Algeria. Only one questionnaire was returned from Albania, Egypt, Portugal and Yugoslavia and, accordingly, no results are provided for these countries.

Respondents were mostly physicians aged 35 to 50 years, though an appreciable proportion were older in Israel and younger in Syria and Turkey (Table 1). Most respondents were hospital-based neurologists. For Syria, questionnaires originated from a single university hospital in Damascus.

Child neurologists were especially numerous in Italy, and paediatricians and psychiatrists accounted for the majority of respondents in Tunisia. The majority of practitioners reported seeing over 50 patients per year, but physicians seeing a smaller number of patients were especially common in Syria and Tunisia.

Comparison of therapeutic practices

Treatment of partial seizures

For the first-line management of partial seizures, carbamazepine was the preferred drug, with over 80% preference in most countries (Fig. 1). Exceptions were Tunisia, where carbamazepine and valproate were similarly popular, and Malta, where four out of five respondents favoured phenytoin as a first choice. In France, Italy and Tunisia, preferential use of valproic acid was somewhat more common among paediatricians and paediatric neurologists compared to physicians treating mainly adult patients. New antiepileptic drugs were rarely mentioned as first-line options, although seven out of 55 selections in Greece were for oxcarbazepine.

Preferences for second-choice treatment differed widely (Fig. 2), the only consistent finding being the choice of valproic acid in over a third of respondents in most countries. Phenytoin was chosen by a considerable number of physicians in Israel, Syria and Turkey, whereas vigabatrin was the preferred second-line agent in about a third of respondents in France, Italy and Malta. Overall, new antiepileptic drugs were selected for second-line treatment in 67 (48%) out of 140 preferences in Italy, 34 (35%) out of 96 in France, two (6%) out of 31 in Israel, nine (43%) out of 21 in Spain and 23 (47%) out of 49 in Greece.

Treatment of primarily generalized tonic–clonic seizures

Valproic acid was the preferred first-line treatment by the vast majority of respondents in Algeria, France, Greece, Italy, Spain and Turkey, and it was also a popular choice in all other countries except Syria (Fig. 3). Other drugs mentioned frequently included phenobarbital (Algeria, Italy, Tunisia and Syria), phenytoin (Greece, Israel, Malta, Turkey and Syria) and carbamazepine (Israel, Syria and Turkey). The new drugs lamotrigine and oxcarbazepine were selected by only three and eight respondents respectively out of a total of 500.

Preferences for second-line treatment showed re-

Table 1: Characteristics of respondents in the countries participating in the survey. Some questions were answered only by some of the respondents.

	Algeria	France	Greece	Israel	Italy	Malta	Spain	Syria	Tunisia	Turkey
Number of questionnaires distributed	20	320	300	80	1156	8	350	160	300	100
Number of respondents	17	90	52	27	132	5	21	26	89	37
Age										
<35 years	6	7	9	0	11	2	2	15	16	17
35–50 years	11	53	35	13	90	3	15	9	62	16
>50 years	0	30	8	13	30	0	4	2	7	4
Speciality										
Neurologist	13	67	44	25	88	2	14	16	17	30
Paediatrician	0	4	1	2	0	1	0	0	35	2
Psychiatrist	2	6	5	0	2	0	0	4	33	0
Neuropaediatrician	1	12	6	5	43	1	7	0	2	5
Other	0	2	0	0	4	1	0	6	2	0
Number of patients seen yearly										
<10	0	2	0	0	4	0	0	4	22	0
10–50	1	12	19	7	23	3	0	5	27	3
51–100	0	22	15	11	26	0	0	9	13	9
>100	14	54	17	8	75	2	19	8	25	24
Affiliation										
Hospital	16	60	36	25	115	5	20	21	39	34
Community	1	8	6	4	15	0	1	0	0	0
Private clinic	0	30	14	0	29	1	7	8	51	8

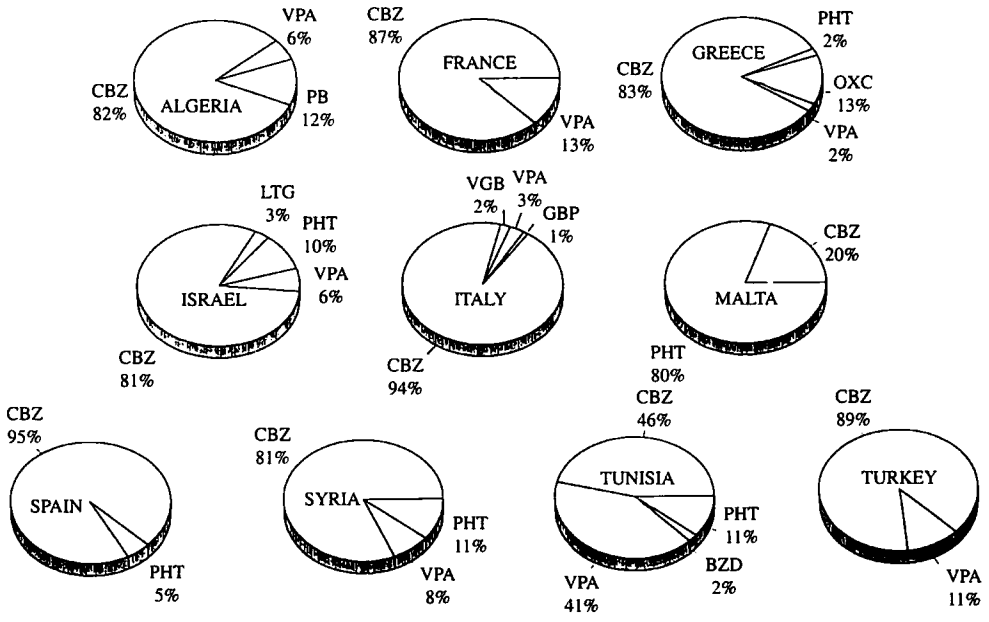

Fig. 1: Drugs used preferentially for the first-line treatment of partial seizures (expressed as percentage of respondents) in the countries included in the survey. Abbreviations: BZD = benzodiazepines; CBZ = carbamazepine; GBP = gabapentin; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; VGB = vigabatrin; VPA = valproic acid.

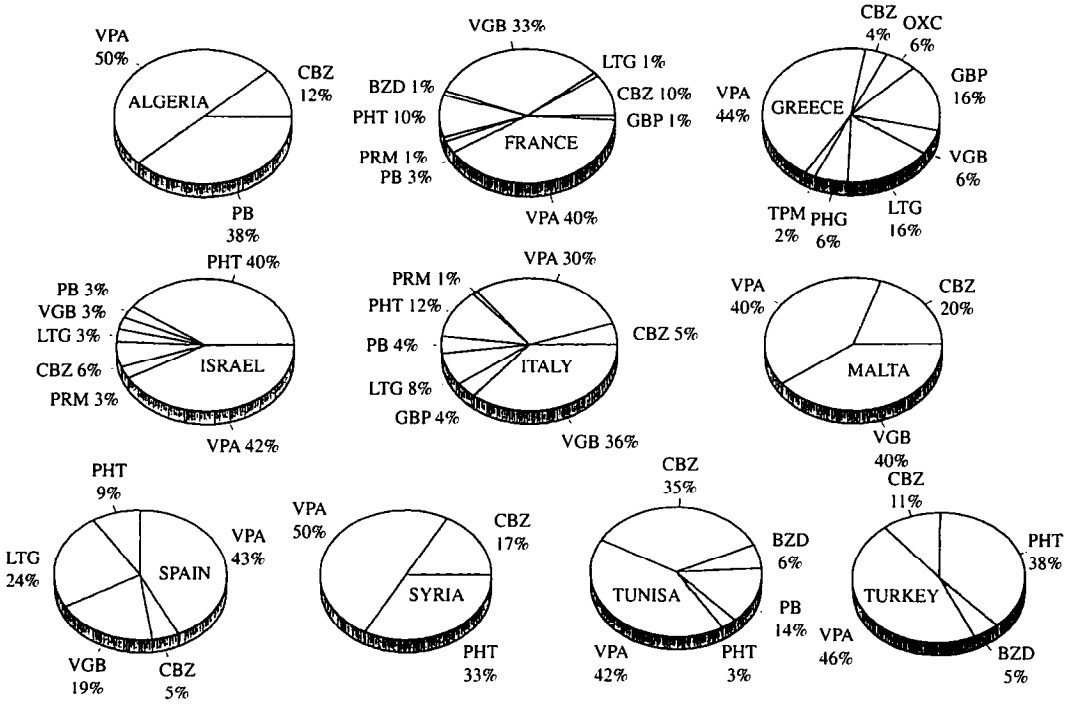

Fig. 2: Drugs used preferentially for the second-line treatment of partial seizures (expressed as percentage of respondents) in the countries included in the survey. PRM = primidone; TPM = topiramate; other abbreviations as in Fig. 1.

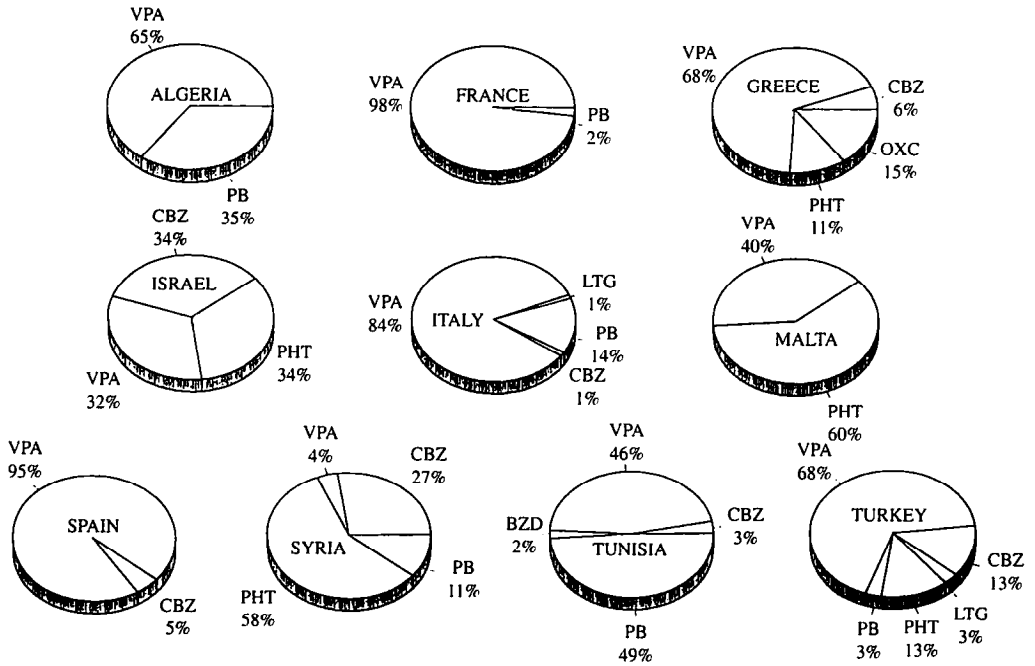

Fig. 3: Drugs used preferentially for the first-line treatment of primarily generalized tonic–clonic seizures (expressed as percentage of respondents) in the countries included in the survey. Abbreviations as in Figs 1 and 2.

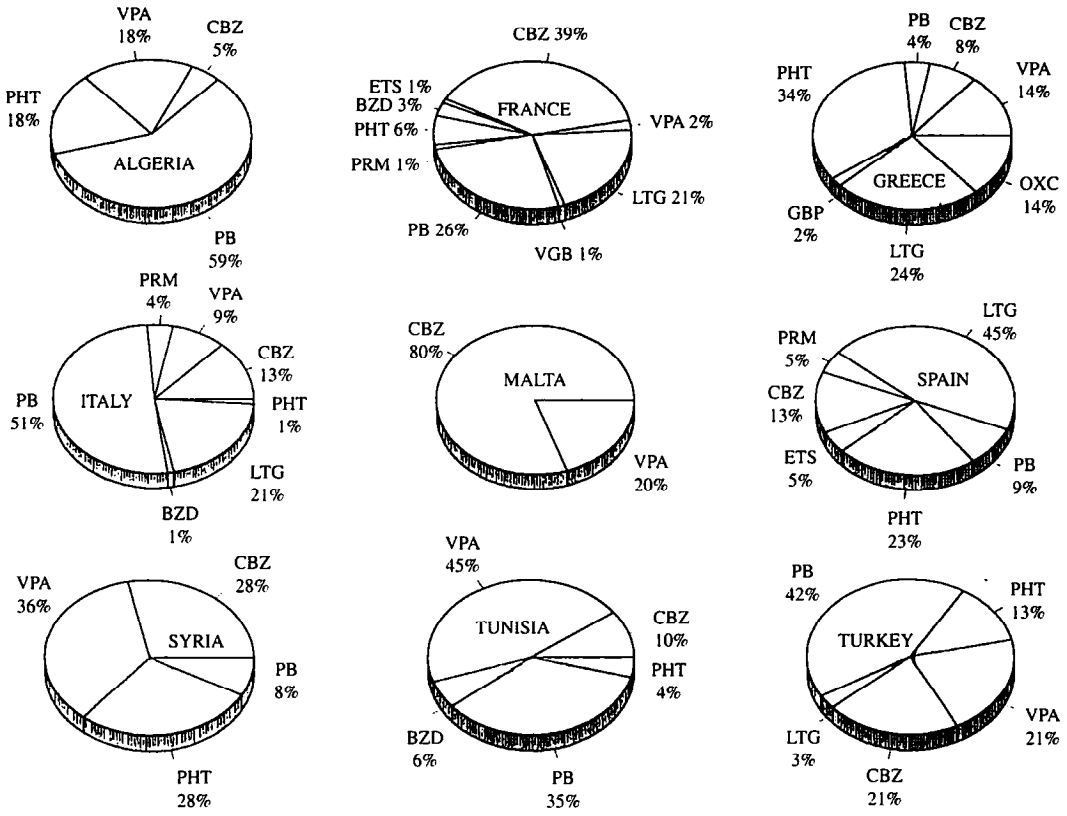

Fig. 4: Drugs used preferentially for the second-line treatment of primarily generalized tonic–clonic seizures (expressed as percentage of respondents) in the countries included in the survey. No data are reported for Israel because this question was not answered by the majority of respondents in that country. ETS = ethosuximide; other abbreviations as in Figs 1 and 2.

markable variation (Fig. 4). Widely favoured options were phenobarbital (Algeria, France, Italy, Tunisia and Turkey), lamotrigine (France, Greece, Italy and Spain), phenytoin (Greece, Spain and Syria) and carbamazepine (France, Malta, Syria and Turkey). As expected, valproic acid was a common second choice for those respondents who did not indicate it as first choice.

Strategies in patients failing on initial monotherapy

Where asked to indicate their preferred approach in patients where initial monotherapy failed, physicians who favoured switching these patients to monotherapy with an alternative drug accounted for 33% of preferences in Syria, 50% in Malta, 52% in Greece, 58% in Turkey, 59% in Algeria, 63% in Italy, 64% in Tunisia, 69% in Israel, 71% in Spain and 77% in France. The remaining respondents indicated that they would add another drug to the pre-existing treatment.

Prophylaxis against recurrence of febrile seizures

The use of pharmacological prophylaxis against the recurrence of uncomplicated febrile seizures is summarized in Table 2. More than 50% of respondents in all countries except Turkey (47.2%) did not prescribe drugs to prevent febrile seizures. Intermittent prophylaxis was used by an appreciable proportion of respondents in Algeria, France, Israel, Italy, Syria, Tunisia and Turkey: this involved mostly rectal administration of a benzodiazepine, though oral benzodiazepines were frequently used in Italy and Tunisia. Interestingly, a small number of physicians used intermittent prophylaxis with valproic acid or phenobarbital.

Continuous prophylaxis with valproate or phenobarbital was prescribed by a relative minority of respondents, especially in France, Syria and Tunisia.

Attitude towards the use of new antiepileptic drugs

The use of new drugs as initial treatment varied widely from one country to another. Many physicians, however, did not provide an answer to this question, possibly because they did not consider the first-line use of a new drug to be acceptable. Among those who provided an answer, the proportion using a new drug as first-line in more than 10% of their patients (with number of respondents in brackets) ranged from 0% (17) in Algeria to 4% (78) in France, 11% (28) in Turkey, 10% (50) in Tunisia, 10% (20) in Israel, 12% (eight) in Syria, 16% (88) in Italy, 20% (20) in Spain and 34% (41) in Greece (plus one of four respondents from Malta). When asked

Table 2: Strategies concerning the use of pharmacological prophylaxis against recurrence of uncomplicated febrile seizures. Drug abbreviations as in Fig. 1.

	Algeria	France	Greece	Israel	Italy	Malta	Spain	Syria	Tunisia	Turkey
Number of respondents	17	82	46	25	124	3	20	23	78	36
Prophylaxis not used	10	47	41	18	86	3	18	13	43	17
Intermittent prophylaxis preferred	4	24	2	6	29	0	2	6	21	15
VPA	1	1	0	0	0	0	0	1	1	2
Oral BZD	2	8	0	3	20	0	2	0	15	0
Rectal BZD	1	11	1	1	8	0	0	1	3	11
BZD (route unspecified)	0	0	1	0	1	0	0	0	1	1
PB	0	0	0	0	0	0	0	4	0	1
Unspecified	0	4	0	2	0	0	0	0	1	0
Continuous prophylaxis preferred	3	11	3	1	9	0	0	4	14	4
VPA	3	9	1	1	8	0	0	0	7	1
PB	0	1	0	0	1	0	0	4	6	3
BZD	0	1	0	0	0	0	0	0	1	0
LTG	0	0	1	0	0	0	0	0	0	0
Unspecified	0	0	1	0	0	0	0	0	0	0

to specify a situation where a new drug was felt to be indicated for first-line treatment, the single most common indication was vigabatrin for infantile spasms, but an appreciable proportion of respondents failed to provide an answer to this question. Overall, vigabatrin in West syndrome (with an indication sometimes restricted to subgroups, such as spasms associated with tuberous sclerosis) was specified by 25 out of 53 respondents in France; seven out of 20 in Greece, four out of 10 in Israel, 31 out of 90 in Italy, one out of three in Malta, 10 out of 18 in Spain, one out of one in Syria, eight out of 16 in Tunisia, and five out of 15 in Turkey. Other indications mentioned by more than four respondents were vigabatrin for partial seizures, sometimes restricted to special subgroups ($n = 9$, France; $n = 22$, Italy), vigabatrin for epilepsy associated with tuberous sclerosis ($n = 7$, Italy; $n = 7$, Turkey), lamotrigine for partial seizures ($n = 5$, Italy) and for one or more types of generalized seizures or epilepsies ($n = 13$, France, $n = 12$, Italy) and felbamate for Lennox–Gastaut syndrome ($n = 13$, Italy).

The only countries where physicians rating the new drugs as more effective than older agents outnumbered those rating the new drugs as equally or less effective were Algeria, Syria and Tunisia, an interesting finding because these were the countries in which new drugs are either not available (Algeria, Syria) or least used (Tunisia). In all countries, new drugs were generally perceived as being better tolerated than older agents, the only exception being Malta where none of the three respondents rated the new drugs as superior in terms of tolerability. High cost and inadequate experience were rated consistently as the main factors limiting the prescription of new drugs. Interestingly, worry about side effects was not considered a major issue, being mentioned by less than 10% of overall respondents.

DISCUSSION AND CONCLUSIONS

This survey provides an interesting comparison of the utilization of antiepileptic drugs in the Mediterranean region. Because of the relatively small proportion of respondents in some countries, results may not be fully representative of national situations, yet they are likely to reflect a segment of the most motivated physicians involved in the treatment of epilepsy in different geographical areas. Respondents covered a wide range of qualifications, from paediatricians to adult neurologists, some with a specialized interest in epilepsy and others with a broader experience in general neurology. The distribution of these qualifications differed somewhat from country to country, an observation which should be taken into consideration when comparing respective therapeutic practices.

The main issues covered in this survey addressed basic decisions concerning clinical management. One is the choice of drugs for the newly diagnosed patient. Based on available evidence, carbamazepine, valproic acid, phenytoin and phenobarbital show similar efficacy against partial seizures and secondarily generalized tonic–clonic seizures[10–18], and these drugs were mentioned as first-line options by most of our respondents. Carbamazepine was the most popular choice for partial seizures, presumably because it is often regarded as having more favourable tolerability compared to some of the other drugs[3]. In recent years, however, valproic acid has been found to be similarly effective and well tolerated in partial epilepsy[4,16,18], which may explain its relative popularity in Tunisia, particularly among paediatricians, and, more generally, its preferential role as a second-line agent in most countries. Phenytoin is a common choice in English speaking countries[6,8] and, accordingly, it was preferred for the first-line treatment of partial seizures by four out of the five Maltese respondents in our survey. For patients with primarily generalized tonic–clonic

seizures, valproic acid was preferred in most countries, although phenytoin, carbamazepine and phenobarbital were also used relatively widely. Valproate, phenytoin, carbamazepine and phenobarbital produced similar remission rates in controlled trials in these patients[10,12,13,16–18], though preferential use of valproic acid may be justified by the observation that some of the other drugs, most notably carbamazepine, are ineffective and may even aggravate other seizure types (particularly absences and myoclonic seizures) which often coexist in epileptic syndromes associated with primarily generalized seizures[4,19].

Another issue investigated was the strategy in patients where initial monotherapy failed. In the past, it was believed that combination therapy had many advantages, and polypharmacy was widely used in the early stages of treatment[20]. In the last two decades, however, the merits of monotherapy have been widely demonstrated[21,22], and recent studies suggest that up to 40–50% of patients where the initial prescribed drug failed may achieve freedom from seizures by switching to monotherapy with an alternative agent[23–25]. This was probably recognized by the numerous physicians who favoured alternative monotherapy in these patients. Advocates of combination therapy, however, were present in all countries, and a proportion of respondents ranging from 21% in Israel to 67% in Syria stated that their usual policy is to add a second drug when initial monotherapy fails. There is no doubt that some patients where sequential monotherapies failed may do well on a drug combination, but how early polytherapy should be tried is obviously a matter of controversy among practising physicians[1,26].

In recent years, evidence has accumulated that recurrence of simple uncomplicated febrile seizures does not increase the risk of subsequent epilepsy, and therefore continuous pharmacological prophylaxis is generally not indicated in these patients[27,28]. Most physicians in our survey complied with this recommendation, although in some countries continuous prophylaxis is still prescribed by an appreciable number of practitioners. Intermittent prophylaxis with oral[29] or, preferably, rectal[28,30] diazepam is a reasonable option in some patients and was frequently adopted in some countries. On the other hand, there seems to be no rationale for intermittent use of phenobarbital or valproic acid[27], which were advocated by a small number of respondents.

One section of the questionnaire was devoted to the attitude towards the use of new drugs. In all countries surveyed, new drugs were very rarely mentioned as agents of choice. However, vigabatrin was often preferred as a second-line treatment against partial seizures in France, Italy and Malta, whereas lamotrigine was often indicated as a second-line treatment against primarily generalized seizures in most European countries. When asked to specify a condition where a new drug was felt to be indicated for first-line treatment, the most common indication was vigabatrin for infantile spasms, in agreement with suggestions made in the recent literature[31]. Many physicians in Italy mentioned felbamate for Lennox–Gastaut syndrome, a surprising finding because first-line use of this drug is not an approved indication due to the risk of aplastic anaemia and liver toxicity[31]. Overall, the survey revealed some scepticism towards the value of new drugs, although there was a common perception that the latter may offer some advantages in tolerability. Interestingly, new drugs were considered to be more effective than older agents by a high proportion of respondents only in North African countries, where new drugs are either not available or least used. In agreement with recent concerns[32], cost was widely considered a major factor limiting use of the new agents.

In conclusion, this survey provides a general overview of prescribing practices among physicians treating epilepsy in Mediterranean countries. Some similarities between countries were observed, but there were also differences which could not entirely be ascribed to local availability of drugs or their cost. Significant differences between individual physicians, as well as some inappropriate or questionable therapeutic practices, were also evident within individual countries. These results may be useful for the planning of further drug utilization studies, for the implementation of educational activities at national and international level, and for the design of trials aimed at comparing different therapeutic approaches.

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